REMARKS

The Applicants again wish to thank the Examiner for his courtesy during a telephonic interview on December 18, 2003.

Claims 1-49, 65-88, 104-118, and 155-158 are pending. Claim 158 has been amended to eliminate the term "in need thereof" as being unnecessary. All pending claims stand rejected.

None of the above changes raise any issue of patentability. Both before and after the above changes, the invention was described in full, clear, concise, and exact terms and met all conditions for patentability under 35 USC 101 *et seq*. The scope of the claims of any resulting patent (and any and all limitations in any of said claims) shall not under any circumstances be limited to their literal terms, but are intended to embrace all equivalents. Accordingly, under no circumstances whatsoever may these claims be interpreted as:

1. having been altered in any way for any reason related to patentability;

2. having been narrowed;

3. a concession that the invention as patented does not reach as far as the original, unamended claim;

4. a surrender of any subject matter as a condition of receiving a patent; and/or,

5. estopping applicants from asserting infringement against every equivalent, whether now known or later developed, foreseen or unforeseen.

Applicants also emphasize that the decision to address the Examiner's suggestions via claim amendment with the understandings set forth above is not in any way intended to avoid the "gatekeeping" role of the PTO with regard to the examination and issuance of valid patents for patentable inventions.

I. JUDICIALLY CREATED DOCTRINE OF OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

The Examiner has maintained the rejection of claims 1-49, 65-88, 104-118, and 155-158 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 95-97, 99-172, and 174 of the Erion *et al.* patent, U.S. Patent No. 6,312,662, for the reasons set forth in the Office Action of September 16, 2002. In that Office Action, the Examiner said:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because the core structure of the cyclic phosphate prodrug overlaps substantially, specifically when the variable Y is oxygen. Additionally, the identity of variable W, W', V, and Z are all substantially overlapping. The examiner notes the major difference between the instant composition claims and the patented claims is in the scope of the heteroatoms attached to the phosphorus in the ring structure. In the instant invention the heteroatoms are selected from oxygen or amine linkages, however the patent limits the heteroatoms to the phosphorus atom to oxygen. The use of this class of compounds to affect a liver related condition is also seen to be obvious in view of claim 174 of the Erion et al. patent. It would have been obvious to the skilled artisan that these compositions of matter and the method for administering the same to affect a liver related condition are indeed prima facie obvious and to neglect to advance an obviousness double patenting rejection is to encourage the unjustified or improper extension of the "right to exclude" granted by a patent. (9/16/02 Office Action pp. 3-4)

The Applicants respectfully traverse this rejection.

Although an obviousness-type double patenting determination relies on a comparison with the claims in the Erion *et al.* patent, the obviousness-type double patenting determination parallels the guidelines for an obviousness determination. M.P.E.P. § 804. Therefore, the Examiner bears the initial burden of establishing a *prima facie* case of obviousness-type double patenting. The Applicants respectfully submit that the Examiner has not presented a *prima facie* case of obviousness-type double patenting.

The Applicants respectfully submit that a person of ordinary skill in the art would not find that any claim in this Application is an obvious variation of claims 95-97, 99-172, and 174 of the Erion *et al.* patent. Although the structures of both inventions share an overlapping cyclic phosphonate structure, they differ in terms of M groups. A person of ordinary skill in the art would not find the required chemical modifications from the structures claimed by the Erion *et al.* patent to the structures claimed in the current invention to be obvious.

As explained during the telephonic interview on December 18, 2003, the novelty of the current invention lies in the fact that there is a **double transformation**. As stated in the Detailed Description of the Invention, the present invention is directed toward **prodrugs of prodrugs**:

> The invention is directed to the use of new cyclic 1,3-propanyl phosph(oramid)ate esters which are converted to phosphate, phosphoramidate, or thiophosphate containing compounds by P450 enzymes found in large amounts in the liver and other tissues containing these specific enzymes. The phosphates, phosphoramidates and thiophosphates are then hydrolized (by alkaline phosphatase, for example) to produce the free hydroxy, amine, or thiol, respectively. This methodology can be applied to various drugs and to diagnostic imaging agents which contain -OH, $-NHR^2$, or -SH functionality. In effect, this methodology provides ***a prodrug*** (cyclic 1,3-propanyl phosph(oramid)ate esters) ***of a prodrug*** (phosphate, phosphoramidate, or thiophosphate) ***of a drug*** (contains -OH, $-NHR^2$ or -SH). p. 17, line 24 – p. 18, line5 (emphasis added).

Clearly, there are two steps involved in the current invention: 1) cyclic 1,3-propanyl phosph(oramid)ate esters are converted to phosphate, phosphoramidate, or thiophosphate containing compounds by P450 enzymes and then 2) the phosphates, phosphoramidates and thiophosphates are hydrolized (by alkaline phosphatase, for example) to produce the free hydroxy, amine, or thiol, respectively.

The Erion *et al.* patent generally claims M groups that are nucleosides and nucleoside analogs that are primarily oncolytic and antiviral compounds. The compounds in the *Erion et al.* patent claims are active in the phosphorylated form. The nucleoside compounds of the Erion *et al.* patent are effective in the liver, because they are generally created in the liver and generally not transported out of the liver, just transformed there. Although the specification of the Erion *et al.* patent may not be used to prove obviousness-type double patenting, the portions of the specification supporting the claims may be "considered when addressing the issue of whether or not a claim in the application defines an obvious variation of an invention claimed in the patent." M.P.E.P. § 804.

Here the Detailed Description of the Invention of the Erion *et al.* patent shows that the Erion *et al.* drugs are active in the phosphorylated form.:

> The invention is directed to the use of new cyclic phosph(on)ate ester methodology which allows compounds to be efficiently converted to phosph(on)ate containing compounds by p450 enzymes found in large amounts in the liver and other tissues containing these specific enzymes. This methodology can be applied to various drugs and to diagnostic imaging agents. More

> specifically, the invention is directed to the use of prodrug-esters of highly charged phosphate, phosphoramidate, and phosphonate containing drugs that undergo non-esterase-mediated hydrolysis reactions to produce the phosphate, phosphoramidate, and phosph(on)ate containing compounds. '662 patent, Col. 17, lines 9-20.

In contrast, the compounds of the present invention are not nucleosides and are not known to be active in the phosphorylated form. The compounds of the present invention can be used as oncolytic and antiviral agents, but they may also be useful in treating other diseases. In fact, the compounds of this invention have the ability to leak out from the original location in the hepatocytes. This is noted in the specification in several places including the following:

> Cancers outside the liver may also exhibit CYP3A4 activity whereas normal tissue surrounding the tumor is devoid of activity. Tumors that metastasize to the liver from non-P450-expressing organs (e.g. breast) often do not have P450 activity. Prodrugs of the invention, however, are still suitable for treatment of these tumors since the drug is produced in normal hepatocytes and depending on the drug, can diffuse out of the hepatocyte and into the tumor. p. 35, lines 1-6.

> Accordingly, the group M represents a group that as part of a compound of formula I enables generation of a biologically active compound in vivo by conversion to MH via the corresponding M-PO_3^{2-}, M-P(O)$(NHR^6)_2$, or M-P(O)$(O^-)(NHR^6)$. The atom in M attached to phosphorus may be O, S or N. The active drug may be MH or a metabolite of M-H useful for treatment of diseases in which the liver is a target organ, including diabetes, hepatitis, liver cancer, liver fibrosis, malaria and metabolic diseases where the liver is responsible for the overproduction of a biochemical end products such as glucose (diabetes), cholesterol, fatty acids and triglycerides (atherosclerosis). Moreover, M-H may be useful in treating diseases where the target is outside the liver in tissues or cells that can oxidize the prodrug. p. 55, lines 9-18.

> Selective breakdown of the drug by the liver, since the liver is the site which has the highest levels of the P450 isoenzymes that catalyze the oxidative cleavage of the prodrugs of formula 1, is envisioned to result in high liver drug concentrations. In some cases, the drug will remain predominantly in the liver due to high protein binding or due to metabolic processes (e.g. glucoronidation reactions) that convert the drug to metabolites that are retained by the liver. In other cases, the drug will diffuse out of the liver and

> enter the blood stream and subsequently other tissues. p. 60, lines 20-26.

As can be seen by looking at the specifications of both this Application and the Erion *et al.* patent claims, the compounds of the present invention differ from those of the Erion *et al.* patent in terms of the biological activity of the phosphorylated compound. The Erion *et al.* patent claims makes it clear that the drug becomes biologically active when it is phosphorylated. Again, this is supported by the specification of Erion *et al.*:

> Parent drugs of the form MH, which are phosphorylated to become the biologically active drug are well suited for use in the prodrug methodology of the present invention. There are many well known parent drugs of the form MH which become biologically active via phosphorylation. '662, Col. 28, lines 3-8.

In the present invention, the phosphorylated compounds are biologically inactive, and this is also supported by the specification:

> Various kinds of parents drugs can benefit from the prodrug methodology of the present invention. It is preferred that the prodrug phosph(oramid)ate moiety be attached to a hydroxy, amine, or thiol on the parent drug. In many cases the parent drug will have many such functional groups. The preferred group selected for attachment of the prodrug is the group that is most important for biological activity and is chemically suitable for attachment of the prodrug moiety. Thus, the phosph(oramid)ate moiety will prevent the prodrug from having biological activity. An inactive prodrug should limit systemic side effects because higher drug concentrations will be in the target organ (liver) relative to non-hepatic tissues. The amine should have at least one N-H bond, and preferably two. p. 34, lines 6-15.

In view of the fact that the present invention is in effect a double prodrug of a drug that is not active in a phosphorylated form, a person of ordinary skill in the art would not find the claims of the current Application obvious in view of claims 95-97, 99-172, and 174 of the Erion *et al.* patent. Therefore, the Applicants respectfully request withdrawal of the double patenting rejection.

Therefore, the Applicants respectfully request withdrawal of the double patenting rejection.

II. THE 35 U.S.C. 103(a)/102(e) REJECTION

The Examiner has maintained the rejection of claims 1-49, 65-88, 104-118, and 155-158 as being obvious over the Erion *et al.* patent, U.S. Patent No. 6,312,662, for the reasons set forth in the Office Action of September 16, 2002. In that Office Action, the Examiner said:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because the core structure of the cyclic phosphate prodrug overlaps substantially, specifically when the variable Y is oxygen. Additionally, the identity of variable W, W', V, and Z are all substantially overlapping. The examiner notes the major difference between the instant composition claims and the patented claims is in the scope of the heteroatoms attached to the phosphorus in the ring structure. In the instant invention the heteroatoms are selected from oxygen or amine linkages, however the patent limits the heteroatoms to the phosphorus atom to oxygen. The use of this class of compounds to affect a liver related condition is also seen to be obvious in view of claim 174 of the Erion et al. patent. It would have been obvious to the skilled artisan that these compositions of matter and the method for administering the same to affect a liver related condition are indeed prima facie obvious and to neglect to advance an obviousness double patenting rejection is to encourage the unjustified or improper extension of the "right to exclude" granted by a patent. (9/16/02 Office Action pp. 5-6)

The Applicants respectfully traverse this rejection.

The Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness.

The Examiner bears the initial burden of establishing a *prima facie* case of obviousness, and until such a showing is made, Applicants are under no obligation to present evidence of non-obviousness. *See In re Piasecki*, 223 U.S.P.Q. 785, 787-88 (Fed. Cir. 1984)(acknowledging that the PTO bears the initial burden of establishing a *prima facie* case of obviousness.). To establish a *prima facie* case, the PTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. *See In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Second, the proposed modification of the prior art must have had a reasonable likelihood of success,

determined from the vantage point of a skilled artisan at the time the invention was made. *See Amgen, Inc. v. Chugai Pharm. Co.*, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir 1991). Lastly, the prior art reference or combination of references must teach or suggest all the limitations of the claims. *See In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). It is well established that the teachings or suggestions, as well as the reasonable expectation of success, must come from the prior art, not from the applicant's disclosure. *See In re Vaeck*, 20 U.S.P.Q. 1438, 1442 (Fed. Cir. 1991).

As explained above and during the telephonic interview of December 18, 2003, a person of ordinary skill in the art would not find the invention of the current application obvious in view of the Erion *et al.* patent. The novelty of the current invention lies in the fact that there is a **double transformation**. In other words, the present invention is directed toward **prodrugs of prodrugs**.

The Erion *et al.* patent discloses M groups that are nucleosides and nucleoside analogs that are primarily oncolytic and antiviral compounds. The compounds in the *Erion et al.* patent are active in the phosphorylated form. The nucleoside compounds of the Erion *et al.* patent are effective in the liver, because they are generally created in the liver and generally not transported out of the liver, just transformed there.

In contrast, the compounds of the present invention are not nucleosides and are not known to be active in the phosphorylated form. The compounds of the present invention can be used as oncolytic and antiviral agents, but they may also be useful in treating other diseases. In fact, the compounds of this invention have the ability to leak out from the original location in the hepatocytes.

It is clear that the compounds of the present invention differ from those of the Erion *et al.* patent in terms of the biological activity of the phosphorylated compound. In addition, the present invention is directed toward prodrugs of prodrugs.

It is highly unlikely that a person of ordinary skill in the art would be motivated by the Erion *et al.* patent, which discloses prodrugs of nucleoside and nucleoside analogs, to make a prodrug of a prodrug of a drug MH, which is not a nucleoside. This would basically require two transformations to make the drug in the body. There is simply no motivation or suggestion in Erion *et al.* to do so.

In addition, even if a person of ordinary skill in the art was motivated to make the required chemical modifications, that person would not have a reasonable likelihood of success. There is no reason to believe that the substitution of non-nucleoside M groups for the nucleosides and nucleoside analog M groups used in Erion *et al.* would result in compounds that can successfully treat diseases of the liver or metabolic diseases where the liver is responsible for the overproduction of a biochemical end product.

In view of the fact that the present invention is in effect a double prodrug of a drug that is not active in a phosphorylated form, a person of ordinary skill in the art would not find the invention of the current Application obvious in view of the Erion *et al.* patent.

Therefore, the Applicants respectfully request withdrawal of the 103(a)/102(e) rejection.

III. THE 35 U.S.C. 103(a) REJECTION

The Examiner has maintained the rejection of claims 1-49, 65-88, 104-118, and 155-158 as being obvious over the Erion *et al.* patent, U.S. Patent No. 6,312,662, for the reasons set forth in the Office Action of September 16, 2002.

In the Office Action of September 16, 2002 the Examiner said that he believed that the current claims 1-49, 65-88, 104-118, and 155-157 were "drawn to a phosphate containing compound wherein the active agent represented by the variable M is etoposide." (9/16/02 Office Action p. 6). The Examiner also believed that claim 158 "is drawn to a method for treating diseases of the liver using a compound of claim 1." (9/16/02 Office Action p. 6).

The Examiner cited the factors from *Graham v. John Deere*, and then went on to say:

> The Erion patent is seen to disclose compounds wherein a phosphate-containing compound wherein the active agent is intended to affect hyperlipidemic conditions, see claims 95 and 96. In column 32, the compound etoposide is specifically set forth as compounds suitable for conversion to compounds of formula I. The structure of formula I in claim 95 is seen to overlap substantially with the instantly claimed invention. Compounds in which two single bonds of oxygen attached directly to the phosphorus atom form the ring structure of the instant invention must be noted. In column 21, lines 61 through column 22, line 17, the prior art clearly sets forth the use of compounds sharing the same chemical core as that which the applicant claims, for treating liver diseases and associated conditions.

> It would have been obvious to one having ordinary skill in this art at the time the invention was made to obtain a cyclic phosphorus containing compound wherein all atoms attached directly to said phosphorus to form a ring are oxygen atoms and the biologically active agent is the saccharide derivative etoposide, because the Erion et al. patent discloses same as indicated supra. It requires little to find motivation to formulate compositions as applicant claims because the structural core of the prior art compounds represents a species of the broad genus applicant claims in the instant application. The method for treating liver disease or an associated condition is also seen to be disclosed in the prior art patent as set forth supra and the invention as claimed is indeed prima facie obvious in view of the Erion et al. patent. (9/16/02 Office Action pp. 6-7)

The Applicants respectfully traverse this rejection.

As explained in the telephonic interview of December 18, 2003 and in more detail below in Section IV, the "etoposide" statements in the '662 patent are not prior art to the current Application.

Therefore, the Applicants respectfully request withdrawal of the 103(a) rejection.

IV. EXAMINER'S RESPONSE TO APPLICANTS' PREVIOUS ARGUMENTS

The Examiner feels that the Applicants made three arguments:

> 1) that the instantly claimed structure differs from the structure of the '662 patent in terms of M groups; 2) that the instantly claimed compounds and the compounds described by the '662 patent differ in terms of biological activity of the phosphorylated compound; and 3) that the reference to etoposide at columns 32-33 of the '662 patent is not prior art. (Office Action p. 4)

The Examiner disagrees with the Applicants' arguments saying:

> The '662 patent teaches "Oncolytic drugs such as etoposide, topotecan, taxol, etc, that contain a biologically important hydroxyl or oncolytic drugs such as mitomycin, anthracylin antibiotics (e.g. dioxorubicin) that contain a biologically important amino group or oncolytic drugs that contain a sulfhydryl moiety are suitable drugs for conversion to compounds of formula 1." See column 32, lines 45-67; column 33, lines 1-15; columns 6-7. The compounds of the '662 patent and the compounds of the instantly claimed invention are both seen to read upon structures wherein the M group is etoposide. Since the Office does not have the facilities for preparing the claimed materials and comparing when with prior art inventions, the burden is on applicant to show a novel or

> unobvious difference between the claimed product and the product of the prior art...In regards to the exclusion of portions of the '662 patent as prior art, the '662 patent has a different inventive entity and is a continuation-in-part of Application No. 09/263,976, filed on March 5, 1999. The instantly claimed invention does not have the benefit of priority beyond the September 8, 1999 filing date of Provisional Application 60/153,128. In the absence of some proof of a secondary nature to obviate the rejection as set forth in the Office Action dated September 16, 2002, or of some specific limitations which would tip the scale of patentability in favor of the instantly claimed invention, the instantly claimed compounds are indeed obvious in view of the prior art.

As explained above and during the telephonic interview on December 18, 2003, the novelty of the current invention lies in the fact that there is a **double transformation**. As stated in the Detailed Description of the Invention, the present invention is directed toward **prodrugs of prodrugs**:

> The invention is directed to the use of new cyclic 1,3-propanyl phosph(oramid)ate esters which are converted to phosphate, phosphoramidate, or thiophosphate containing compounds by P450 enzymes found in large amounts in the liver and other tissues containing these specific enzymes. The phosphates, phosphoramidates and thiophosphates are then hydrolized (by alkaline phosphatase, for example) to produce the free hydroxy, amine, or thiol, respectively. This methodology can be applied to various drugs and to diagnostic imaging agents which contain -OH, $-NHR^2$, or -SH functionality. In effect, this methodology provides ***a prodrug*** (cyclic 1,3-propanyl phosph(oramid)ate esters) ***of a prodrug*** (phosphate, phosphoramidate, or thiophosphate) ***of a drug*** (contains -OH, $-NHR^2$ or -SH). p. 17, line 24 – p. 18, line5 (emphasis added).

Clearly, there are two steps involved in the current invention: 1) cyclic 1,3-propanyl phosph(oramid)ate esters are converted to phosphate, phosphoramidate, or thiophosphate containing compounds by P450 enzymes and then 2) the phosphates, phosphoramidates and thiophosphates are hydrolized (by alkaline phosphatase, for example) to produce the free hydroxy, amine, or thiol, respectively.

1) As explained in the previous Response, although the structures of both inventions share an overlapping cyclic phosphonate structure, they differ in terms of M groups. The '662 patent discloses M groups that are nucleosides and nucleoside analogs that are primarily

oncolytic and antiviral compounds. The compounds in the '662 patent are active in the phosphorylated form. The nucleoside compounds of the '662 patent are effective in the liver, because they are generally created in the liver and generally not transported out of the liver, just transformed there. In contrast, the compounds of the present invention are not nucleosides and are not known to be active in the phosphorylated form. The compounds of the present invention can be used as oncolytic and antiviral agents, but they may also be useful in treating other diseases. In fact, the compounds of this invention have the ability to leak out from the original location in the hepatocytes.

A person of ordinary skill in the art would not find the required chemical modifications from the structures claimed by the '662 patent to the structures claimed in the current invention to be obvious. It is highly unlikely that a person of ordinary skill in the art would be motivated by the '662 patent, which discloses prodrugs of nucleoside and nucleoside analogs, to make a prodrug of a prodrug of a drug MH, which is not a nucleoside. This would basically require two transformations to make the drug in the body. There is simply no motivation or suggestion in '662 to do so.

In addition, even if a person of ordinary skill in the art was motivated to make the required chemical modifications, that person would not have a reasonable likelihood of success. There is no reason to believe that the substitution of non-nucleoside M groups for the nucleosides and nucleoside analog M groups used in '662 would result in compounds that can successfully treat diseases of the liver or metabolic diseases where the liver is responsible for the overproduction of a biochemical end product.

2) As explained in the previous Response, the Detailed Description of the Invention of the '662 patent shows that the '662 drugs are active in the phosphorylated form.:

> The invention is directed to the use of new cyclic phosph(on)ate ester methodology which allows compounds to be efficiently converted to phosph(on)ate containing compounds by p450 enzymes found in large amounts in the liver and other tissues containing these specific enzymes. This methodology can be applied to various drugs and to diagnostic imaging agents. More specifically, the invention is directed to the use of prodrug-esters of highly charged phosphate, phosphoramidate, and phosphonate containing drugs that undergo non-esterase-mediated hydrolysis reactions to produce the phosphate, phosphoramidate, and

> phosph(on)ate containing compounds. '662 patent, Col. 17, lines 9-20.

In contrast, the compounds of the present invention are not nucleosides and are not known to be active in the phosphorylated form. The compounds of the present invention can be used as oncolytic and antiviral agents, but they may also be useful in treating other diseases. In fact, the compounds of this invention have the ability to leak out from the original location in the hepatocytes. This is noted in the specification in several places including the following:

> Cancers outside the liver may also exhibit CYP3A4 activity whereas normal tissue surrounding the tumor is devoid of activity. Tumors that metastasize to the liver from non-P450-expressing organs (e.g. breast) often do not have P450 activity. Prodrugs of the invention, however, are still suitable for treatment of these tumors since the drug is produced in normal hepatocytes and depending on the drug, can diffuse out of the hepatocyte and into the tumor. p. 35, lines 1-6.

> Accordingly, the group M represents a group that as part of a compound of formula I enables generation of a biologically active compound in vivo by conversion to MH via the corresponding M-PO_3^{2-}, M-P(O)$(NHR^6)_2$, or M-P(O)$(O^-)(NHR^6)$. The atom in M attached to phosphorus may be O, S or N. The active drug may be MH or a metabolite of M-H useful for treatment of diseases in which the liver is a target organ, including diabetes, hepatitis, liver cancer, liver fibrosis, malaria and metabolic diseases where the liver is responsible for the overproduction of a biochemical end products such as glucose (diabetes), cholesterol, fatty acids and triglycerides (atherosclerosis). Moreover, M-H may be useful in treating diseases where the target is outside the liver in tissues or cells that can oxidize the prodrug. p. 55, lines 9-18.

> Selective breakdown of the drug by the liver, since the liver is the site which has the highest levels of the P450 isoenzymes that catalyze the oxidative cleavage of the prodrugs of formula 1, is envisioned to result in high liver drug concentrations. In some cases, the drug will remain predominantly in the liver due to high protein binding or due to metabolic processes (e.g. glucoronidation reactions) that convert the drug to metabolites that are retained by the liver. In other cases, the drug will diffuse out of the liver and enter the blood stream and subsequently other tissues. p. 60, lines 20-26.

As can be seen by looking at the specifications of both this Application and the '662 patent claims, the compounds of the present invention differ from those of the '662 patent in terms of the biological activity of the phosphorylated compound. The '662 patent claims makes it clear that the drug becomes biologically active when it is phosphorylated. Again, this is supported by the specification of '662:

> Parent drugs of the form MH, which are phosphorylated to become the biologically active drug are well suited for use in the prodrug methodology of the present invention. There are many well known parent drugs of the form MH which become biologically active via phosphorylation. '662, Col. 28, lines 3-8.

In the present invention, the phosphorylated compounds are biologically inactive, and this is also supported by the specification:

> Various kinds of parents drugs can benefit from the prodrug methodology of the present invention. It is preferred that the prodrug phosph(oramid)ate moiety be attached to a hydroxy, amine, or thiol on the parent drug. In many cases the parent drug will have many such functional groups. The preferred group selected for attachment of the prodrug is the group that is most important for biological activity and is chemically suitable for attachment of the prodrug moiety. Thus, the phosph(oramid)ate moiety will prevent the prodrug from having biological activity. An inactive prodrug should limit systemic side effects because higher drug concentrations will be in the target organ (liver) relative to non-hepatic tissues. The amine should have at least one N-H bond, and preferably two. p. 34, lines 6-15.

In addition, as stated in the Detailed Description of the Invention, the present invention is directed toward prodrugs of prodrugs:

> The invention is directed to the use of new cyclic 1,3-propanyl phosph(oramid)ate esters which are converted to phosphate, phosphoramidate, or thiophosphate containing compounds by P450 enzymes found in large amounts in the liver and other tissues containing these specific enzymes. The phosphates, phosphoramidates and thiophosphates are then hydrolized (by alkaline phosphatase, for example) to produce the free hydroxy, amine, or thiol, respectively. This methodology can be applied to various drugs and to diagnostic imaging agents which contain -OH, $-NHR^2$, or -SH functionality. In effect, this methodology provides ***a prodrug*** (cyclic 1,3-propanyl phosph(oramid)ate esters) ***of a***

> ***prodrug*** (phosphate, phosphoramidate, or thiophosphate) ***of a drug*** (contains -OH, -NHR^2 or -SH). p. 17, line 24 – p. 18, line5 (emphasis added).

In view of the fact that the present invention is in effect a double prodrug of a drug that is not active in a phosphorylated form, a person of ordinary skill in the art would not find the claims of the current Application obvious in view of claims 95-97, 99-172, and 174 of the '662 patent.

3) The Applicants agree that the instantly claimed Application has a priority date of September 8, 1999, the filing date of the Provisional Application. The Applicants are not saying that the current Application has an earlier priority date, but instead that the "etoposide statements" are not entitled to a priority date earlier than September 8, 1999.

As discussed during the Interview on December 18, 2003, the Applicants have forwarded sections of the 09/263,164 application to the Examiner. This section of the 09/263,164 application clearly shows that the "etoposide statements" were not in the application filed on March 5, 1999. The "etoposide statements" were not added until the filing of the application that became the '662 patent on September 8, 1999. In other words, the application (later the '662 patent) that contained the "etoposide statements" and the priority application in this case were filed on the same day. Therefore, the "etoposide statements" can not be used as prior art against the current Application.

CONCLUSION

In conclusion, Applicants respectfully submit that all pending claims are in condition for allowance. The Examiner is invited to contact Applicants' undersigned Representative if it is believed that prosecution may be furthered thereby.

Respectfully Submitted,

Date: 12/30/03

By: Diana L. Bush

Diana L. Bush, Ph.D., Esq.
Reg. No. 51,109

Paul, Hastings, Janofsky & Walker LLP
3579 Valley Centre Drive
San Diego, CA 92130
Direct Dial: (858) 720-2885
Facsimile: (858) 720-2555